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Effectiveness and cost-effectiveness of treatment with third generation agents in advanced Non-Small-Cell Lung Cancer: a systematic review

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Introduction

1.1 Background

Lung cancer is the most common cause of cancer related death for men and women in the western world (1). Forty percent of these deaths occur in people younger than 65 years of age. Hence, the loss to society as well as the economic burden to the health care system is substantial. Approximately 85% of all lung cancer cases are of the subtype non-small cell lung cancer (NSCLC) (2). Many patients are diagnosed in an advanced stage (III or IV) for which surgical resection is not recommended and radiation therapy is mainly palliative.

Over the past decades, research focusing on chemotherapeutic treatments for patients with incurable NSCLC have led to only modest gains in survival. Nevertheless, trials have generally supported the use of two chemotherapeutic drugs rather than one in terms of response rates, survival and quality of life. A recent systematic review of the literature concerning the effectiveness in terms of response rates, survival, progression free survival and quality of life of new drugs such as docetaxel, gemcitabine, paclitaxel, pemetrexed, and vinorelbine concluded that none of these new drugs were clearly superior when used in combination with a platinum agent (3). In addition, they concluded that the survival advantage of platinum based doublets over non-platinum combinations was modest. Another important conclusion was that chemotherapeutic treatment beyond four to six cycles impedes quality of life without prolonging life.

The modest (but still important) improvements in the care for NSCLC patients are achieved at considerable costs. Therefore, the economic evaluation of new chemotherapeutic drugs has become very important for health policy makers who are charged with allocating limited funds to various health care programs. In 2002, a review of economic evaluations of expensive drugs for NSCLC treatment, including docetaxel, gemcitabine, paclitaxel and vinorelbine was published (4). The authors concluded that, contrary to the general opinion at that time, expensive drugs such as vinorelbine and gemcitabine were cost-effective. The evidence with respect to cost-effectiveness requires updating, especially because of the intensive research efforts in the last decade to improve treatment outcome for NSCLC patients.

In this report, we firstly summarize the available evidence with respect to the effectiveness of docetaxel, paclitaxel, gemcitabine and vinorelbine in Chapter 2. Because there was limited evidence available on the direct comparison of the four third generation drugs among each other, we did a systematic search to answer this question. In Chapter 3, we present a systematic review of the evidence with respect to the cost-effectiveness of docetaxel, gemcitabine, paclitaxel, vinorelbine and pemetrexed. In the following, we first describe the agents of interest with respect to their indicated use, method of administration and adverse effects. The description is taken from the Dutch Pharmaceutical Compass and from www.longkanker.info (5;6) .

1.2 Description of the agents of interest

According to the Dutch clinical guidelines the standard treatment of patients stage IV is a third generation agent in combination with a platinum agent, for example: 1000 mg/m² gemcitabine (third generation agent) on day 1 and 8 in combination with 100mg/m² cisplatin (platinum agent) on day 1 and 21. However, there is no recommendation for which third generation agent and which platinum agent. As a consequence, many treatment combinations are used in daily clinical practice: third generation agents are used as single therapy, with an additional platinum agent, or in combination with each other.

Additionally, there is no consensus in treatment dosage schemes in daily practice (7).

Docetaxel

Docetaxel (Taxotere) is indicated as treatment in combination with a (non-) platinum agent, mainly for second line treatment after response failure of prior chemotherapy. It is also indicated as first line treatment in combination with cisplatin in metastatic or locally advanced NSCLC patients. Administration is usually via infusion once every 3 weeks. Possible adverse effects include allergic reactions presenting as flushing, skin reactions, itching, chest tightness, back pain, difficulty breathing, fever or chills, swelling, weight gain, stomach upsets, alopecia, cardiac irregularities and tiredness. Contraindications include severe allergic reaction, low white blood cell count due to bone marrow damage ('myelosuppression'), severe liver disease, pregnancy or breastfeeding.

Paclitaxel

Paclitaxel (Taxol) is indicated as treatment in combination with a (non-)platinum agent, for either first-line NSCLC treatment or after response failure of prior chemotherapy. Doses are given by infusion, along with steroids given prior to administration of paclitaxel to help prevent allergic reactions. Adverse events may include allergic reaction, blood disorders, fever, unusual bleeding or unexplained bruising, heart problems, high or low blood pressure, numbness, joint or muscle pain, liver disorders, nausea, diarrhoea, sore mouth and tongue, hair loss, skin reactions and swelling at the injection site.

Gemcitabine

Gemcitabine (Gemzar) is indicated as treatment in combination with a (non-) platinum agent, and is mainly used for first-line treatment of locally advanced or metastatic NSCLC. Gemcitabine is given by intravenous infusion once weekly for 3 weeks. Adverse events may include myelosuppression, lethargy, flu-like symptoms, rashes, nausea and vomiting, and hair loss. Treatment should be stopped if there is evidence of hemolytic anemia.

Vinorelbine

Vinorelbine (Navelbine) is indicated as treatment in combination with a (non-) platinum therapy, either in first-line treatment or after response failure of prior chemotherapy in locally advanced or metastatic NSCLC. It is currently administered in an outpatient setting on a weekly basis by intravenous infusion, though an oral version has been developed. Adverse effects include myelosuppression, nausea and vomiting, constipation, weakness, peripheral neuropathy, alopecia and injection site pain.

In 2006, the Dutch Pharmaceutical Compass published a report on the assessment of vinorelbine for the treatment of stage IIIB/IV NSCLC. The results of a combination therapy of vinorelbine and cisplatin were comparable with the results of combination therapies of docetaxel and gemcitabine with cisplatin, although it was not clear in which line of treatment (8).

The recommended dose administration is 25 mg/m² per week in combination with cisplatin (100 mg/m² per 4 weeks) and 25-30 mg/m² per week as monotherapy (8).

Platinum agents used in combination with the third generation agents:

Cisplatin

Cisplatin (Cisplatin and Platosin) is a platinum based cytotoxic drug, mainly used in combinations with non-platinum agents. Before and/or after the cisplatin infusion, extra intravenous fluids are administered to ensure adequate hydration before, during and after the administration of cisplatin. This is needed to prevent kidney damage due to the platinum levels. Therefore, cisplatin is mainly administered by infusion in an outpatient setting. Adverse effects include nausea, vomiting, alopecia, kidney damage and hearing impairment.

Carboplatin

Carboplatin (Carbosin en Paraplatin) is a platinum based cytotoxic drug, mainly used in combinations with non-platinum agents. An advantage of carboplatin compared to

cisplatin is that the intravenous administration of extra fluids is not necessary. Carboplatin can even be administered in an outpatient setting. Adverse effects include nausea, thrombocytopenia, neutropenia, leucopenia and anemia.

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Effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non- small cell lung cancer

Evidence on the effectiveness of the third generation chemotherapeutic drugs docetaxel, gemcitabine, vinorelbine and paclitaxel has recently been systematically retrieved and summarized by Goffin et al. (2010). This systematic review included studies until 2007 (3). Questions addressed in this review that are relevant for the current report are:

Question 1. Does chemotherapy improve outcomes compared to best supportive care (BSC)?

Question 2. Does doublet chemotherapy consisting of a platinum agent plus a third generation agent improve outcomes compared to doublets using older agents?

Question 3. Does triplet chemotherapy improve outcomes compared to doublet chemotherapy and does doublet chemotherapy improve outcomes compared to a single agent?

Question 4. Is a single third generation agent superior to BSC or to another single third generation agent?

Question 5. Does doublet chemotherapy consisting of a platinum agent improve outcomes compared with non-platinum combination chemotherapy?

Question 6. Which doublet chemotherapy regimen consisting of a platinum agent plus a third generation agent is most effective in improving clinical outcomes?

Whereas relatively good evidence was available for most of the questions addressed in the review (questions 1 to 5), the authors concluded that there was limited evidence on possibly superiority of any of the new drugs compared to the others (question 6).

In section 2.1, the presently available evidence concerning questions 1 to 6 is summarized. This summary is largely based on Goffin et al, but we also refer to the original studies, the original reviews and the meta-analyses. For questions 1-5 we used additional literature (until 2010), question 6 is only based on the review by Goffin et al., in other words, only based on the literature until 2007. Question 6 will be updated in this review.

In section 2.2 and 2.3 we present the methods and results, respectively, of the search strategy that was used to update the evidence on possible superiority of any of the new agents.

2.1 Overview of the available evidence regarding chemotherapy until 2010

Q1. Does chemotherapy improve outcomes compared to best supportive care (BSC)?

The most recent version of the Dutch guidelines (2010) supports the use of chemotherapy as first-line treatment option for patients stage IIIB/IV and a WHO performance score of 0-2 (7). A meta analysis of the Non-Small Cell Lung Cancer Collaborative Group of 2008 comparing chemotherapy in addition to best supportive care and best supportive care alone. They found an improvement in survival of 23% (HR= 0.77; 95% CI 0.71-0.83), equivalent to an absolute increase in median survival of 1.5 months (from 4.5 months to six months), for patients receiving chemotherapy in addition to best supportive care. The meta-analysis included all types of drugs as chemotherapy, but the effect was not influenced by type of drug (9).

Q2. Does doublet chemotherapy consisting of a platinum agent plus third generation agent improve outcomes compared to doublets using older agents?

A meta analysis by Baggstrom et al. (2007) comparing third generation platinum based doublets to second generation platinum based doublets of six studies, showed a one-year survival-rate risk difference of 6% (95% CI: 0.02,0.10) corresponding to one-year survival rates between 39-48% in the third generation platinum based doublets versus survival rates between 27-41% in the second generation platinum-based doublets (10). Goffin et al. discussed four trials discussing this question in their review. One found a statistically significant improvement in survival for a third generation platinum based doublet (docetaxel-cisplatin) compared to a second generation platinum based doublet (vindesine-cisplatin) (11). The three remaining trials showed inconsistent results (12-14), as two trials reported a higher median survival in favor of second generation regimens (7.7 months versus 9.0 months (12) and 10 months versus 11.1 months (14)) and another trial reported a median survival of 18.7 versus 15.7 months in favor of third generation regimens (13). In summary, there is some evidence for the superiority of third generation agents compared to second generation agents.

Q3. Does triplet chemotherapy improve outcomes compared to doublet chemotherapy and does doublet chemotherapy improve outcomes compared to a single agent?

The third generation agents, either in combination with a platinum agent or as a single agent, are recommended for NSCLC treatment in the Dutch guidelines (7). Whereas the use of a platinum agent plus a third generation agent is considered standard treatment for advanced NSCLC patients, the use of a single third generation agent is considered to minimize toxicity in specific patient subgroups, such as patients aged 70 years or older, patients who have a performance status of ≥2, and patients for whom platinum therapy is contraindicated (3). In the meta analysis by Hotta et al. (2004), third generation-platinum based doublets (vinorelbine-cisplatin, docetaxel-cisplatin) were compared to single third generation agents (vinorelbine alone, docetaxel alone), using the data of

eight trials (15). Doublet therapy was found to have a statistically significant improved response rate of 28-47% versus 11-20% for single therapy (OR:2.32; 95% CI:1.68, 3.20), and a statistically significant better median survival of 28-47 weeks versus 21-42 weeks for single therapy (HR 0.87; 95% CI: 0.80, 0.94) compared to single therapy, but was also associated with increased adverse effects such as nephrotoxicity, nausea and vomiting. In 2007, a Cochrane review based on 65 trials (including the 8 trials analyzed by Hotta et al.) confirmed these findings (16). In the pooled analysis of the included trials (n=33), comparing a doublet regimen with a single-agent regimen, a significant increase in tumor response (OR 0.42, 95% CI: 0.37- 0.47) and one-year survival (OR 0.80, 95% CI 0.70 to 0.91, 13 trials) was observed in favor of the doublet regimen. A pooled analysis of trials comparing triplet regimens to doublet regimens resulted in an increase in the tumor response rate (OR 0.66, 95% CI 0.58- 0.75) in favor of the triplet regimen, but this effect was not found in one-year survival (OR 1.01, 95% CI 0.85-1.21). Both Goffin et al. and Delbaldo et al. concluded that addition of a third chemotherapeutic agent provided no survival benefit but only increased toxicity (3;16).

Q4. Is a single third generation agent superior to BSC or to another third generation agent?

In the meta-analysis by Baggstrom et al., the one-year survival benefit of single third generation agents was 7% compared to best supportive care, corresponding with one-year survival rates between 25-32% and 14-23% for single third generation agent and best supportive care, respectively. In the same study, platinum plus second generation doublets showed better response rates than single third generation agents, although the one year survival remained equal (10).

Goffin et al. mentioned three trials which focus on comparisons between single third generation agents in patients 70 years or older (17-19). None of these studies found a significant survival benefit for one agent over the other, although one trial reported improved response rate with docetaxel over vinorelbine (19).

In a Dutch study (20), age was not a predictor of side-effects of paclitaxel-carboplatin and gemcitabine-carboplatin, from which the authors concluded that the decision to give either single or doublet therapy should not be based on age alone.

Q5. Does doublet chemotherapy consisting of a platinum agent improve outcomes compared to non-platinum combination chemotherapy?

The use of a platinum agent, such as cisplatin and carboplatin, is recommended in doublet therapy over doublets with non-platinum agents (15;21). In addition, it can be concluded from two recent meta-analyses that cisplatin-based combinations resulted in a slightly better response rate and a survival advantage over carboplatin-combinations (22;23). One meta-analysis found a survival advantage for cisplatin in combination with a third generation agent versus carboplatin in combination with a third generation agent in a non-squamous population (24).

2.2 Overview of the available evidence regarding the individual agents until 2007

Q6. Which doublet chemotherapy regimen consisting of a platinum agent plus a third generation agent is most effective in improving clinical outcomes?

At present, doublet therapy consisting of a third generation agent and a platinum based agent is considered standard therapy (7). However, it is still unclear whether any third generation therapy is favored over another. Goffin et al., mentioned two meta-analyses comparing the third generation agents among each other (25;26). The meta analysis by Le Chevalier et al. showed a statistically significant progression-free survival benefit for patients assigned to gemcitabine-based treatment compared to other doublets with carboplatin and a third generation agent (HR: 0.88; 95% CI: 0.82-0.93; median progression-free survival 5.1 months versus 4.4 months). On the other hand, the overall survival benefit was small and not statistically significant (HR: 0.93; 95% CI: 0.86, 1.01; median survival not reported) (25). The meta analysis by Douillard et al. (n=4), showed

an improved survival (HR 0.89; 95% CI: 0.82, 0.97; median survival not reported) and less toxicity and adverse events in favor of docetaxel regimens compared to vinorelbine regimens (26).

Out of nine trials discussed by Goffin et al., only one trial (27) observed a statistically significant survival benefit, progression free survival benefit and response rate for one of the agents over the other, that is docetaxel-cisplatin over comparator arm vinorelbine-cisplatin. Five out of nine trials reported quality of life outcomes (QOL). Only one trial found statistically significant improvements in QOL, for docetaxel compared to vinorelbine (27).

To conclude, although the studies reviewed by Goffin et al. reported differences in survival outcomes, the results were inconsistent. Therefore, we updated the search in order to add the latest results regarding the comparative effectiveness of the four agents of interest among each other.

2. 2 Methods

Search strategy

As this was the most recent and relevant systematic review on third generation agents, we updated the systematic review of Goffin et al. using the same search strategy (see Table 1 in the Appendix).

We searched the bibliographic databases PubMed, EMBASE.com and CENTRAL (via the Cochrane Library, Wiley) from November 1st 2007 to September 27th 2010. Search terms included controlled terms from MeSH in PubMed and Emtree in EMBASE.com as well as free text terms. We used free text terms only in CENTRAL database from the Cochrane library. Search terms expressing Non-Small-Cell Lung Carcinoma were used in combination with search terms comprising expensive chemotherapies. In PubMed and EMBASE.com, search results were limited by search terms indicating specific study designs: (clinical trial including 'controlled', 'randomized', 'evaluation study', 'review').

Selection phase

To identify relevant studies, two independent reviewers (MLB and EPJ) screened the studies resulting from the search strategy, based on title and abstract. Studies were considered eligible for inclusion if they:

- Evaluated new agents in a phase III randomized controlled trial (RCT), a systematic review, a meta-analysis or an evidence-based report.
- Included adult or elderly NSCLC patients receiving chemotherapy as first- or second-line therapy.
- Reported on at least one of the following outcomes: overall survival, progression-free survival, quality of life, overall response rate.
- Were full text articles written in either Dutch or English.

We excluded the following studies:

- Studies that included new agents, but the primary objective of the study was to evaluate a non-eligible agent or therapy.
- Publication types other than phase III trials, systematic reviews or meta-analyses, such as editorials, letters, legal cases, interviews.

If necessary, the full text article was checked for the eligibility criteria. Any disagreements were resolved through a consensus procedure. The references of the identified articles were searched for relevant publications.

2.3 Results

Search results

The literature search generated a total of 2817 references: 878 in PubMed, 1563 in EMBASE.com and 376 in CENTRAL. After removing duplicates of references that were selected from more than one database, 1930 papers remained. Out of these 1930 papers, 182 met the inclusion criteria at first screening based on title and abstract. These 182 papers assessed the agents of interest for effectiveness, but only 8 studies evaluated these agents among each other. These 8 studies were considered eligible for inclusion, of

which 2 were included in a meta-analysis which resulted from the search as well (28). The flow chart of the search and selection procedure is presented in Figure 1 in the Appendix.

Description of the studies

Among the 6 remaining studies, 2 were meta-analyses (28;29), 1 was a review (30), and 3 were clinical trials (31-33). All the available studies compared doublet regimens, containing a third generation agent and a platinum agent.

Which doublet chemotherapy regimen consisting of a platinum agent plus a third generation agent is most effective in improving clinical outcomes? An update.

The meta-analysis by Grossi et al. (28) (n=45) showed comparable response rates among the third generation agents in doublets with platinum agents. Comparing gemcitabine-containing regimens with gemcitabine-free regimens in a pooled analysis (n=23) resulted in an OR for progression of 0.86 (95% CI: 0.77-0.95; 992 events of progressive disease versus 1094 events out of 3 340 and 3 341, respectively). In other words, a 14% lower risk of progression was found among patients receiving gemcitabine compared to patients receiving other third generation drugs. A 9% lower risk of progression (OR: 0.91; 95% CI: 0.80, 1.04; 726 and 771 events out of 2 317 and 2 325, respectively) was seen in the patients receiving docetaxel regimens compared to patients receiving docetaxel-free regimens (n=12), although this risk reduction was not significant. Paclitaxel- containing regimens (n=16) showed a 22% higher risk of progression, which was statistically significant (OR: 1.22, 95% CI: 1.09-1.37; 984 events and 869 events out of 2 768 in both arms). No difference in risk of progression was observed between vinorelbine-containing regimens and vinorelbine-free regimens. Finally, although the differences in events of progressive disease were statistically significant, no significant differences were observed in response rates between any of the

regimens. As an explanation for this finding, the authors stated that in general, response rates are less correlated with overall survival than progression rates (28).

The meta analysis by Gao et al. (29), comparing gemcitabine plus platinum (either cisplatin or carboplatin) regimens to vinorelbine plus platinum regimens, found no significant differences in response rates (RR 0.91, 95% CI 0.81-1.03), nor in one-year survival (RR 1.06, 95%CI 0.96-1.18). Vinorelbine plus platinum led to more frequent grade 3 or 4 neutropenia, nephrotoxicity, constipation and phlebitis, while gemcitabine plus platinum led to more grade 3 or 4 thrombocytopenia. Considering this difference in toxicity profiles, the authors conclude that the choice for either gemcitabine or vinorelbine in addition to platinum may be guided by the patients' tolerance.

The review by Joshi et al. (30) concluded that gemcitabine-platinum is superior to other third generation agents in terms of progression free survival and survival. However, this review was not conducted in a systematic way and included phase II studies as well.

The trial by Chang et al. (31), which was not included in the meta-analyses mentioned above, found similar results comparing gemcitabine plus platinum (GC) (1000 mg/m² gemcitabine on days 1,8 and 15 + 80 mg/m² cisplatin on day 15) to vinorelbine plus platinum (VC) (20 mg/m² vinorelbine on days 1,8 and 15 + 80 mg/m² cisplatin on day 15). They observed no statistically significant differences in response rates (GC 38% versus 31%, *P* for Fisher's exact test =0.622), progression free survival (6.6 months (GC) versus 5.3 months (VC), *P* for log rank test= 0.443) and median survival (12.9 months (GC) versus 9.0 months (VC), *P* for log rank test= 0.4197), but they observed a significant increase in all grade thrombocytopenia in the gemcitabine plus platinum arm.

The trial by Tan et al, comparing vinorelbine-cisplatin (first cycle (intravenous): 25 mg/m² vinorelbine + 80 mg/m² cisplatin on day 1 and 60 mg/m² vinorelbine on day 8, following cycles (oral): 30 mg/m² vinorelbine on day 1 and 80 mg/m² vinorelbine on day 8) to docetaxel-cisplatin (75 mg/m² docetaxel+75 mg/m² cisplatin on day 1) observed no statistically significant difference in time to treatment failure (hazard ratio (HR) 0.872, 95% CI 0.710-1.072 in favor of docetaxel), median survival (vinorelbine 9.9

months, 95% CI 8.41-11.6; docetaxel 9.8 months, 95% CI 8.8-11.5) or quality of life (data not presented) (32).

A direct comparison between gemcitabine and paclitaxel regimens was made by Treat et al. (33). This trial compared gemcitabine-carboplatin (GC) (1000 mg/m² gemcitabine + carboplatin AUC 5.5 on day 1, 1000 mg/m² gemcitabine on day 8), paclitaxel-carboplatin (PC) (225 mg/m² paclitaxel +carboplatin AUC 6.0 on day 1) and gemcitabine-paclitaxel (GP) (1000 mg/m² gemcitabine + 200 mg/m² paclitaxel on day 1, 1000 mg/m² gemcitabine on day 8) regimens. Only small and non-significant differences between treatment arms in median survival (GC 7.9 months, GP 8.5 months, PC 8.7 months, *P* for log rank test= 0.693) , time to progression of disease (GC 4.3 months, GP 4.5 months, PC 4.7 months, *P* for log rank test= 0.912) and response rate (GC 25.3 %, GP 32.1%, PC 29.8%, no log rank test) were found. Toxicity was not significantly different between the arms: hematological events, such as grade 3 thrombocytopenia, were mainly observed in the gemcitabine-carboplatin arm, non-hematological events were mainly observed in the paclitaxel-carboplatin arm as well as the gemcitabine-paclitaxel arm.

Gaps in literature

The search strategy of the present review resulted in a small number of phase III trials comparing docetaxel, paclitaxel, gemcitabine and vinorelbine among each other. Consequently, the evidence to indicate superiority of one of the agents is lacking. More studies comparing these agents among each other is warranted, and ongoing (34).

To determine the optimal treatment strategy, research should focus on targeted therapies such as erlotinib and gefitinib, as well as the supplement of monoclonal antibodies, such as bevacuzimab and cetuximab.

Ongoing research

A total of 61 phase III trials featuring docetaxel are currently registered at the US National Institute of Health (34). Among these are studies focusing on first-line treatment as well as second-line treatment. The studies mainly investigate docetaxel as

reference for newer therapies, such as erlotinib and gefitinib. For gemcitabine, 56 phase III trials are registered assessing first-line treatment strategies. Gemcitabine is mainly compared to vinorelbine, paclitaxel and pemetrexed in first-line treatment of patients with advanced NSCLC, or as reference in trials assessing erlotinib as first-line treatment in patients with an EGFR mutation. A total of 69 phase III trials are currently ongoing for the clinical assessment of paclitaxel and 34 phase III trials for vinorelbine. These numbers are overlapping as more trials nowadays are comparing these agents among each other.

Additionally, many trials are comparing docetaxel, paclitaxel, gemcitabine and vinorelbine supplemented by new biologicals, such as the monoclonal antibodies bevacuzimab and cetuximab (34).

3

Cost-effectiveness of paclitaxel, docetaxel, gemcitabine, pemetrexed and vinorelbine in non small cell lung cancer

Whereas systematically summarized evidence on the effectiveness of docetaxel, gemcitabine, paclitaxel and vinorelbine is from recent date, evidence with respect to the cost-effectiveness of third generation agents requires updating.
Reviews available in the literature up till now mainly included studies evaluating third generation agents compared to best supportive care or compared to second generation agents. Because second-generation drugs are no longer recommended, we chose to include in this report only studies comparing third generation agents among each other or to BSC.

3.1 Overview of the available evidence until 2010

In 2002, a review of economic evaluations of expensive drugs for NSCLC treatment, including docetaxel, gemcitabine, paclitaxel and vinorelbine was published (4). The authors concluded that, compared to BSC, expensive drugs were not only cost-effective (vinorelbine and gemcitabine) but cost-saving in some cases (second generation agents). This completely contradicted the general opinion at that time. Another review conducted by NICE in 2001, evaluated the cost-effectiveness of these four agents of interest as well, and found all of the novel agents to extend life at reasonable costs (£6 249-£15 283 per LYG) (35). However, due to a lack of head-to-head phase III trials, all regimens were compared to best supportive care only. A more recent study (36), reviewed all literature available up till June 2007 in which the cost-effectiveness of any drug treatment for NSCLC was evaluated. Most included studies concerned second- and third generation agents. Although few of the included studies utilized methodological approaches

consistent with recommended guidelines, the authors concluded that drug therapy compared to no treatment appears to provide reasonable value for money. Given the absence of systematic reviews that specifically address the comparison of third generation drugs among each other as well as a lack of cost-utility studies in existing reviews, we felt that an update of the health economic evidence is warranted.

3.2 Methods

Search strategy

We performed systematic searches in the bibliographic databases PubMed, EMBASE.com and Economic Evaluations (via the Cochrane Library, Wiley) from inception to October 11 2010. Search terms included controlled terms from MeSH in PubMed and EMtree in EMBASE.com as well as free text terms. We used free text terms only in the Economic Evaluations database from the Cochrane library. Search terms expressing non-small-cell lung carcinoma were used in combination with "AND" and with search terms comprising expensive chemotherapies and terms for cost-effectiveness. The search strategy is presented in Table 2 of the Appendix.

Selection phase

To identify relevant studies, two independent reviewers (MLB and EPJ) screened the studies resulting from the search strategy, based on title and abstract. Studies were considered eligible for inclusion if they:

- Evaluated the agents of interest as one of the main topics in a full economic evaluation, more specifically in a cost-effectiveness or cost-utility study.
- Reported on at least one of the following outcomes: costs and quality of life, or costs and survival.
- Were full text articles written in either Dutch or English.

Studies were excluded, if they:

- Included new agents, but the primary objective of the study was to evaluate a non-eligible agent or therapy.
- Included a new agent, but the only other comparator arm was a non-eligible agent.
- Solely focused on the cost-effectiveness of the treatment of metastases in stead of primary tumors.

The results of the screening of both reviewers were compared, and any disagreements were discussed. If disagreement remained, a third reviewer was consulted in order to reach consensus. The references of the selected articles were searched for relevant publications.

Data assessment

The full text of each of the selected studies was obtained for further review. Two reviewers (MLB and VC) independently evaluated the methodological quality of the full economic evaluations using the British Medical Journal Checklist for authors and peer reviewers of economic submissions, consisting of 35 items (37). Again, the results were compared and disagreements were discussed in order to reach consensus. The objective of a critical appraisal is to assess whether the included studies describe methods, assumptions, models and potential biases in a way that is transparent and supported by the evidence, in order to enable appraisal by any critical reader. Although no checklist has been formally validated, the BMJ checklist by Drummond et al. (1996) is recommended for Cochrane reviews (38).

As the BMJ checklist by Drummond does not provide for the assessment of modeling studies, we supplemented the evaluation of methodological quality with a framework proposed by Philips et al. This framework consists of three dimensions of quality: structure, data and consistency, subdivided in several questions for critical appraisal, such as the rationale for model structure, justification of identification of data, and the extent to which consistency of the results with other models is discussed.

3.4 Results

Search results

The literature search generated a total of 368 references: 113 in PubMed, 188 in EMBASE.com and 67 in Economic Evaluations from the Cochrane Library. After removing 146 duplicates that were included in more than one database, 222 papers remained. Out of these 222 papers, 21 met the inclusion criteria, of which 4 were conference abstracts only, 2 were not available in full text in time after 2 requests, 1 was only available in Portuguese, 1 was a report assessing a manufacturers' economic evaluation with no references, and 1 was a comment on an other included study. The flow chart of the search and selection process is presented in Figure 2 of the Appendix.

Description of the studies

Among the 12 remaining studies 3 were reviews, 6 were cost-effectiveness studies and 3 were cost-utility studies. We present a summary of the economic evaluations by type of treatment: first-line treatment (4 studies), maintenance therapy (1 study), and second-line treatment (4 studies). An overview of the economic evaluations, separately for first- and second-line treatment, is presented in Table 1 and 2, respectively.

The results of the assessment of the methodological quality for first- and second-line treatment and maintenance therapy, as well as the assessment of the modeling studies, are presented in Table 3, 4 and 5 of the Appendix. A few items were consistently underreported, such as 'are the ranges over which the variables were varied for sensitivity analysis justified?' (39-44), 'were details of statistical tests and confidence intervals of stochastic data reported?' (39-44) and 'were quantities of recourse use reported separately from their unit costs?' (41;42;45;46).

Among the four studies focusing on first-line treatment one was a model-based cost-utility study, the others were cost-effectiveness studies alongside a trial. One study focused on gemcitabine-cisplatin versus pemetrexed-cisplatin (41), one study focused on

gemcitabine-cisplatin versus vinorelbine-cisplatin, paclitaxel-cisplatin, paclitaxel-carboplatin and docetaxel-cisplatin (43), one study focused on paclitaxel-cisplatin versus gemcitabine-cisplatin and gemcitabine-paclitaxel (46), and one study focused on gemcitabine-docetaxel versus docetaxel alone (47). The study focusing on maintenance therapy was a cost-effectiveness study, comparing pemetrexed to observation (42).
Four studies focused on second-line treatment. Out of these four studies, two studies were cost-effectiveness studies alongside a trial and two studies were cost-utility studies based on a model. All four studies focused on docetaxel. Two studies compared docetaxel to best supportive care (BSC) (40;44), one study to pemetrexed (45), and one study to pemetrexed and erlotinib (39), the latter being beyond the scope of this report.

Table 1. Overview of included studies for first-line treatment

Author, year	**Characteristics** (type, perspective, time horizon, discounting)	**Population**	**Treatment** (*administration*, frequency x dose (in mg/m²) /cycle)	**Data input:**	**Reported outcomes**	**Authors' conclusion, Reviewers' remarks**
Klein (41)	Model-based CEA and CUA US payer perspective Time horizon: 2 years No discounting, but 3-5% varied in sensitivity analysis	Chemotherapy-naive patients, stage IIIB/IV NSCLC, with non-squamous patients as subgroup of primary interest.	**PEM-CIS** *NR* 1x500 -1x 75 **GEM-CIS** *NR* 2x 1250 -1x 75	**Clinical data:** head-to head trial data for survival, progression-free survival and response rates. **Resource use/ costs:** chemotherapy costs from max. reimbursement assuming average doses, costs of administration and monitoring from claims database of the year 2002.	**ICERs**(US$): Non-squamous: LYG: 83 537 QALYs : 132 829 All: LYG: 104 577 QALYs: 179 597	**Conclusion:** Considering a US$100 000 threshold value for LYG, pemetrexed-cisplatin is a cost-effective option compared to gemcitabine-cisplatin in a non-squamous population. **Remarks:** it is not clear whether costs of hospitalization are included. Costs associated with serious adverse events and costs for second-line treatment are considered equal for both treatment arms, which is unlikely to be true daily clinical practice. This may have biased the results against pem-cis.
Neymark (46)	CEA of a multicenter trial Dutch health insurance system Time horizon: 3 years No discounting	NSCLC patients stage IIIB/IV (mainly Dutch patients). N=480	**PAC -CIS** *IV, 3hrs* 1x175 - 1x 80 **GEM-CIS** *IV, <1hr* 2x 1250 -1x 80 **GEM-PAC** *IV, 3hrs* 2x 1250 -1x 175	**Clinical data:** head-to-head trial data: mean survival, by restricted mean analysis (AUC) **Resource use:** trial case reports (drugs) and trial protocol (medical services) **Costs:** costs of clinical stay, transfusions and radiotherapy from the national reimbursement tariffs by CTG valid for 2002, for costs of hospitalization a charge-to-cost ratio based on CTG tariff of day clinic stay, cost of drugs from Dutch Pharmaceutical Compass.	**Mean survival time (years):** PAC-CIS : 0.94 GEM-CIS : 0.98 GEM-PAC : 0.80 **Total costs** (€): PAC-CIS : 16 662 GEM-CIS: 13 944 GEM-PAC: 17 377	**Conclusion:** The probability that GEM-CIS improves outcome and at the same time reduces costs is 72% compared to PAC-CIS. GEM-PAC is not likely to improve survival (6%) or reduce costs (12%) **Remarks:** As their total costs are an underestimation, the authors do not present an ICER , but a cost-effectiveness plane. National tariffs were used in stead of costs, resource use for drugs was based on trial reports from different hospitals and trial protocols were used regarding the medical resources.
Lees (43)	CEA based on two trials UK health care system perspective, Time horizon: Randomization until death No discounting	Locally advanced NSCLC stage IIIB/IV. The trial with GEM vs DOC and PAC arms had mainly stage IV pts. 2 trials, total N=1266	**GEM-CIS** *NR* 2x1250 - 1x 100 **PAC-CIS**, *IV 24hrs* 1x175 -1x 75 **PAC-CAR**, *IV 3hrs* 1x225 -1xAUC dose **DOC-CIS** *NR* 1x75-1x75 **VIN-CIS** *NR* NR	**Clinical data:** two head to-head trials: Survival, time to progression **Resource use**: trial data for chemotherapy and administration, hospitalization was based on incidence of side effects. **Costs:** chemotherapy costs from British national formulary, hospital costs from UK national schedule of reference costs, administration and health professionals cost from UK-based source of unit costs in health care. All costs relate to the year 2000.	(ref =GEM-CIS**)** **Incr. PFS (yrs):** PAC-CIS -0.083 PAC-CAR -0.075 DOC-CIS -0.100 VIN-CIS -0.135 **Incr. costs** (£): PAC-CIS 3 506 PAC-CAR 2 907 DOC-CIS 242 VIN-CIS 571	**Conclusion:** In the context of the UK health care perspective, gemcitabine-cisplatin represents a cost-effective treatment for NSCLC compared to novel therapies. **Remarks:** hospitalization costs may be underestimated as not all relevant adverse events were included. All treatments were administered in an outpatient setting, except for paclitaxel-cisplatin. Data regarding the recourse use of radiotherapy, transfusions and concomitant medications was not available, and therefore these costs were assumed equal. In the other trial (gem-cis vs vin-cis), all costs except for chemotherapy and administration were assumed to be equal.
Maniadakis (47)	CEA of a trial Greek national health care perspective Time horizon: Randomization until death No discounting	Advanced/ metastatic NSCLC patients. N=312	**DOC** *NR* 1x100 (N=155) **DOC-GEM** *NR* 1x100-2x2000 (N=157)	**Clinical data:** head-to head trial data for survival, progression-free survival, response rates, and response duration. **Resource use/costs:** head-to head trial data on recourse use was combined with unit costs (2005) of (pre)medication, administration, radiotherapy and hospitalization of the Greek national sources and hospitals database.	(ref= DOC) **Incr. mean survival (months):** DOC-GEM 1.94 **Incr. costs** (€): DOC-GEM 1 542	**Conclusion:** In the Greek national health system setting, docetaxel-gemcitabine is a cost-effective treatment for NSCLC patients, with a ratio about €9 500 per life year gained, in relation to monotherapy with docetaxel alone. **Remarks:** it is not clear why these treatments are relevant, as other treatments especially platinum based regimens, are less expensive and improve survival. Although all costs seem to be included, the differences between treatment arms were not explained in terms of recourse use.

CEA, cost-effectiveness analysis; CUA, cost-utility analysis; NSCLC, non-small-cell lung cancer; PEM, pemetrexed; CIS, cisplatin; GEM, gemcitabine; LYG, life years gained; QALYs, quality adjusted life years; PAC, paclitaxel; IV, intravenous; CTG, College Tarieven Gezondheidszorg; NR, not reported; CAR, carboplatin;, DOC, docetaxel; VIN, vinorelbine; incr., incremental; PFS, progression free survival; 1 €= US$ 1,32 =£ 0,84 on 13-12-2010.

Table 2. Overview of included studies for second-line treatment

Author, year	**Characteristics** (type, perspective, time horizon, discounting)	**Population**	**Treatment** (*administration*, frequency x dose (in mg/m²) /cycle)	**Data input:**	**Reported outcomes**	**Authors' conclusion, Reviewers' remarks**
Leighl (44)	CEA of a trial Canadian health care system perspective Time horizon: randomization until death No discounting	NSCLC patients stage IIIB/IV, with WHO performance status ≤2, previously treated with platinum-based therapy. N=104	**BSC** *NR* NR x 75 **DOC** *IV 1hr* 1 x 75	**Clinical data:** mean survival from head-to head trial data (TAX 317 study) ref **Resource use:** trial an hospital records **costs:** all costs (chemotherapy/administration/palliative care/radiation therapy/toxicity) from trial and hospital records (1999), costs of hospitalization and clinical visits were calculated by hotel approximation method	Incr costs: 10 804 Inc survival: 0.34 **ICER**(CD$): LYG: 31 776	**Conclusion:** The clinical benefits of second-line chemotherapy seem similar in magnitude to those derived from first-line therapy, but the costs of second-line are higher. The ICER is below an acceptable range for health interventions in Canada (CD$53 000 –CD$251 000). **Remarks:** Patients in the docetaxel arm were more likely to be admitted to the acute care setting or a palliative care facility. Use of the perspective of the Canadian provincial health care systems may decrease the cost of care because of the country's centralized, public administration and regulation of drug costs, as patients might use more resources than those in a user-pay system.
Holmes (40)	CEA of a trial UK National Health System perspective Time horizon: 2 years No discounting	NSCLC patients stage IIIB/IV, with WHO performance status ≤2, previously treated with platinum-based therapy. N=104	**BSC** *NR* NR x 75 **DOC** *IV 1hr* 1 x 75	**Clinical data** mean survival form head-to-head trail data, by AUC curve analysis. **Resource use:** trial data **Costs:** source for costs of chemotherapy was NR. Administration costs were based on a study on unit costs and resource use in health care, toxicity costs were based on a study on colorectal cancer, all in year 2000/2001.	Incr. costs: 4 432 Incr survival: 0.32 **ICER** (£) LYG: 13 863	**Conclusion:** Docetaxel 75 mg/m2 in 3-weekly cycles is a cost-effective second-line treatment for pre-treated NSCLC patients, from the perspective of the NHS, in terms of survival gains made for a reasonable increase in costs. **Remarks:** There is uncertainty about chemotherapy costs, and only therapeutic and palliative interventions are considered. In addition, cost estimates were not separately presented from resource use and only incremental costs were reported, which make this study poor in transparency.
Asukai (45)	Model-based CEA and CUA Spanish health care system perspective, Time horizon: 3 years 3% discounting for both costs and benefits	NSCLC patients stage IIIB/IV with predominantly non-squamous population, previously treated with chemotherapy. N=399	**PEM** *IV, <2 hrs* 1 x 500 **DOC** *IV, <2 hrs* 1 x 75	**Clinical data:** model input variables were survival, PFS, and tumor response, based on head-to head trial data (JMEI trial). **Resource use**: head-to-head trial data for chemotherapy and administration, hospitalization was based on side effects. **Costs:** chemotherapy costs from summary of product information, hospital costs from healthcare databases, costs of adverse events, BSC and palliative care were opinion-based. Year of value was not reported.	Incr. costs: 2 334 Incr. LYG: 0.14 Incr. QALYs: 0.10 **ICERs** (€) LYG: 17 225 QALYs : 23 967	**Conclusion:** In the Spanish health care setting, pemetrexed for second-line treatment of patients with NSCLC other than predominantly squamous cell histology is indicated as a cost-effective treatment option compared to the standard docetaxel, based on its superior overall survival benefit and toxicity profile. **Remarks:** costs of adverse events, BSC and palliative care were based on expert opinion surveys of five Spanish clinicians. It was assumed that survival would follow an exponential distribution, although this is very unlikely, as this distribution assumes constant hazards.
Carslon (39)	Model-based CEA and CUA US payer perspective Time horizon: 2 years Costs and effects were discounted at 3%	NSCLC patients stage III/IV, who failed at least one platinum-based treatment. 4 trials, total N=1754	**DOC** *IV 1hr* NR x 150 **PEM** *IV 1 hr* NR x 880 **ERL** *oral* NR x 150	**Clinical data:** Survival and PFS from the 4 trials, utilities from a study based on EQ5D. **Resource use:** AEs were from published (other?) trials, drug use was from the trials. **Costs:** drug costs were from the First Data Bank online database of 2007. Costs of disease progression were based on a study, administration and adverse events were based on CMS physicians fee schedule.	PEM vs DOC ($US) Incr. costs: 4 655 Incr. QALYs: 0 ERL vs PEM Incr.costs: -6782 Incr. QALYs: 0.01 ERL vs DOC Incr. costs: -2127 Incr. QALYs: 0.01	**Conclusion:** Erlotinib is less costly in the treatment of refractory NSCLC in the US compared to alternative treatments, and potentially leads to a slight improvement in QALYs. **Remarks:** Survival and PFS were assumed equal in all arms. QALYs were assumed to be equal in DOC and PEM arms, but not for ERL. These assumptions may not reflect clinical practice. It was not clear how PFS and QALYs were calculated. The four trials differed in their population, in terms of prior treatment and WHO performance status. No costs for prognostic testing of EGFR marker were considered.

Conversion rate on 13-12-2010:1 €= US$ 1,32 =£ 0,84= CD$ 1,33. CEA, cost-effectiveness analysis; NSCLC, non-small-cell lung cancer; WHO, World Health Organization; BSC, best supportive care; NR, not reported; DOC, docetaxel; IV, intravenous; LYG, life years gained; incr., incremental; AUC, area under curve; NHS , national health service; CUA, cost-utility analysis; PEM, pemetrexed; PFS, progression free survival; QALYs, quality adjusted life years; ERL, erlotinib;

First-line treatment

All of the studies focusing on first-line treatment included gemcitabine in one of the treatment arms, either in combination with cisplatin (3 studies) or in combination with docetaxel (1 study). Table 1 provides an overview of all studies for first-line treatment. In table 3 and 4, the costs and benefits reported in the three studies with a gemcitabine-cisplatin arm are presented in detail (41;43;46). Table 3 shows which costs and benefits are included in each study and Table 4 shows total and incremental costs and benefits of the gemcitabine-cisplatin arm and the comparator arm of each study. All studies presented their results in different ways: they used different outcome measures and different currencies from different years. This made a comparison between studies complex. It was remarkable that two studies did not present incremental cost-effectiveness ratios (ICERs) as outcome measure and one study did not report incremental costs and benefits. The ICER is the additional costs per extra unit of effect (48).

Klein et al., assessed the cost-effectiveness of gemcitabine-cisplatin compared to pemetrexed-cisplatin in a general stage IIIB/IV population as well as in patients with non-squamous cell carcinoma. In this subgroup, they found an ICER of US$ 83 537 per LYG for pemetrexed-cisplatin compared to gemcitabine-cisplatin, based on incremental costs of USD 4 509 and incremental life-years of 0.054 (corresponding to 2,6 weeks). The cost-utility analysis resulted in an ICER of US$ 132 829 per QALY gained, based on 0.0339 incremental QALYs and US$ 4 509 incremental costs. In the total group (non-squamous and squamous cell carcinoma) the incremental costs for pemetrexed were higher than in the non-squamous group (US$ 5 072) and LYG and QALYs were lower (LYG: 0.0485, QALYs: 0.0282), resulting in higher ICERs (LYG: US$ 104 577, QALYs: US$ 179 597) (41). In the USA the value of US$ 50 000 per QALY gained is frequently quoted as being the threshold for cost-effectiveness, but a range of US$ 109 000 - US$ 297 000 is more likely to be consistent with societal preferences (49). In this regard, pemetrexed-cisplatin is considered cost-effective compared to gemcitabine-cisplatin, regardless of histological subtype.

Although Klein et al. included all relevant costs from a health care payer perspective, the costs for adverse events within both treatment arms were considered equal. This assumption may have biased the ICERs against pemetrexed-cisplatin, as the trial reported a higher incidence of serious adverse events in the gemcitabine arm. A sensitivity analysis was conducted to address this assumption, resulting in an ICER of US$ 39 000-US$ 44 000, corresponding with a 45%-55% decrease in adverse events for pemetrexed. Costs of chemotherapy were estimated from reimbursement rates and average doses. Other costs were obtained from the PharMetics claims database with ICD codes from 2002. Costs for second-line treatment were also assumed to be equal in both arms (41). Costs associated with hospitalization were not reported separately, but we assume that these costs were incorporated within the costs of administration, monitoring and side effects, since a claim database was used for cost estimation.

Neymark et al. conducted a study in the Netherlands, comparing paclitaxel-cisplatin - which was considered the standard treatment according to the European Organization for Research and Treatment of Cancer (EORTC) in 2005- with gemcitabine-cisplatin and with gemcitabine-paclitaxel (46). For each pairwise comparison, the results were presented in a cost-effectiveness plane, showing the joint distribution of 5000 bootstrap replicates of differences in costs and survival time in years. The authors found a 72% probability that gemcitabine-cisplatin improves survival and reduces costs compared to paclitaxel-cisplatin. Mean survival was similar in both arms (0.94 versus 0.98 years in favor of gemcitabine-cisplatin), which was estimated by restricted mean analysis (46). The differences in costs were explained by the chemotherapy costs, paclitaxel being a more expensive drug than gemcitabine (€8 654 per patient versus €5 234 per patient). Comparing paclitaxel-cisplatin to gemcitabine-paclitaxel resulted in a probability of 82% that gemcitabine-paclitaxel would reduce mean survival while increasing costs. Mean survival was 0.80 years in the gemcitabine-paclitaxel arm versus 0.94 years in the paclitaxel-cisplatin arm with chemotherapy costs of €11 108 and €8 654, respectively. The authors concluded that gemcitabine-paclitaxel is clearly dominated by the standard treatment of paclitaxel-cisplatin.

The third study considering the gemcitabine-cisplatin regimen, is the cost effectiveness study of Lees et al. (2002). They compared gemcitabine-cisplatin to paclitaxel-cisplatin, paclitaxel-carboplatin, docetaxel-cisplatin and vinorelbine-cisplatin using the results of two trials. Overall survival was very similar for the treatment arms containing either docetaxel or paclitaxel, but median survival time was increased for gemcitabine-cisplatin compared to vinorelbine-cisplatin (42 versus 35 weeks; survival times of other arms were not reported). Progression-free survival was reported for all regimens. Gemcitabine-cisplatin resulted in incremental progression free life years ranging from 0.083 to 0.135 (see table 4). Main cost drivers in this study were the costs of chemotherapy and the costs of administration of chemotherapy, as the administration of some drugs requires more hospital time (paclitaxel depending on infusion time, and cisplatin can only be administered in an inpatient setting). All costs were based on national databases (British National Formulary, UK national schedule of reference costs), and resource use and outcomes were based on head-to-head trial data. The authors concluded that the gemcitabine-cisplatin regimen provides value for money relative to other novel regimens. The authors did not report any ICERs, nor any incremental analysis of the treatment regimens. In stead, they presented the incremental costs and incremental progression free survival (see Table 4) (43).

The study by Maniadakis et al. found that gemcitabine-docetaxel is a cost-effective treatment option in the Greek health care setting, compared to docetaxel monotherapy (47). The mean survival difference was almost 2 months in favor of gemcitabine-docetaxel, with total costs that were €1 542 higher than for docetaxel alone. This resulted in an ICER of €9 538 which is far below international thresholds used to accept implementation and reimbursement of new treatments.

Table 3. Overview of included clinical input and costs per study for first-line treatment

Study	Klein (41)	Neymark (46)	Lees (43)	Maniadakis (47)
Parameter				
Survival (months)				
Mean	-	+	-	+
Median	+	_	-	-
Progression free survival				
Mean	-	_	+	-
Median	-	_	-	-
Costs				
Chemotherapy	+	+	+	+
Other medications	+	+	+	+
Administration	+	+	+	?
Hospitalization	+*	+	+	+
Investigations/tests	+	+	_	+
Outpatient visits	+	+	+*	+
Toxicity/ adverse events	+*	±	±	+
Progression/terminal care/ second-line treatment	+*	+	_	+

+, included in analyses; -, not included in analyses; ?, not clear whether included in analyses; +*, included, but assumed equal; ±, only blood transfusions.

[1]Resource use is based on the same trial (50)

[2] Only incremental costs presented, BSC is set at 0

Table 4. Detailed overview of results of those studies on first-line treatment which have gemcitabine-cisplatin as one of the treatment arms.

Study, comparator	Costs			Survival (y)		
	GEM+CIS arm	comparator arm	incremental costs	GEM+CIS arm	comparator arm	incremental survival
Klein et al. (41)				Median survival		
PEM+CIS	$US61 008	$US65 517	$US−4509	0.87	0.98	−0.054[a]
Neymark et al. (46)				Mean survival		
PAC+CIS	€13 944	€16 662	€−2718	0.98	0.94	0.04
PAC+GEM	€13 944	€17 377	€−3433	0.98	0.80	0.18
Lees et al. (43)				Progression-free survival		
PAC+CIS	£5537	£9043	£−3506	0.375	0.292	0.083
PAC+CAR	£5537	£8444	£−2907	0.375	0.300	0.075
DOC+CIS	£5537	£5779	£−242	0.375	0.275	0.100
VIN+CIS[b]	£4477	£5048	£−571	0.808	0.673	0.135

a Incremental survival resulting from running the model. Median survival of both arms presented here was directly taken from the trial and cannot be subtracted to obtain incremental survival.
b The results for VIN-CIS vs GEM-CIS were obtained from another trial.
CAR = carboplatin; **DOC** = docetaxel; **PAC** = paclitaxel; **PEM** = pemetrexed; **VIN** = vinorelbine.

Maintenance therapy

One study was available for maintenance therapy (42). The primary objective was to estimate the cost-effectiveness of maintenance therapy with pemetrexed compared to observation, each in addition to best supportive care, in patients with advanced non-small cell lung cancer (NSCLC) who have completed, without progression, at least four cycles of first-line platinum chemotherapy. The median overall survival for patients treated with pemetrexed compared to observation was 15.5 months versus 10.3 months in the non-squamous group and 13.4 months versus 10.6 months in the total population, both in favor of pemetrexed. Additionally, patients treated with pemetrexed had a longer progression-free survival compared to observation in the non-squamous subgroup (2.6 months), as well as in the total population (1.7 months). Major costs were drug costs as well as costs for serious adverse events. The costs for observation were considered to be zero. Costs for second-line treatment were considered equal in both treatment arms. In the pre-specified subset of patients with non-squamous cell histology, the incremental cost per life-year gained was US$ 122 371 for pemetrexed compared to observation. In all patients with advanced NSCLC regardless of histological subtype, using pemetrexed as maintenance therapy led to an incremental cost per life-year gained of US$ 205 597 compared to observation. The authors concluded that histology is important in targeting the appropriate patients for pemetrexed maintenance therapy, as it is more cost-effective to treat only patients with non-squamous histology with pemetrexed maintenance therapy.

Second-line treatment

All of the studies focusing on second-line treatment included docetaxel in one of the treatment arms, either as a comparator or as the reference agent. Table 2 presents an overview of the studies. Docetaxel is considered an eligible agent for second line treatment as well as the newer agents pemetrexed and erlotinib. An overview of included costs and benefits for all treatment arms of the four studies is presented in Table 5. The total and incremental costs, as well as survival estimates are presented in Table 6.

Holmes et al. and Leighl et al. compared 75 mg docetaxel to BSC, and both found docetaxel to be cost-effective from a health care system perspective (40;44). Both studies considered survival and recourse use based on the same trial, TAX 317 (50), although they used different ways to estimate the key parameters in their analyses. The study by Leighl et al. reported an ICER of CD$ 31 776 per life year gained for the 75 mg docetaxel arm versus BSC. Incremental survival in this study was based on mean survival of the trial data, which was 9.48 months in the docetaxel 75 mg arm and 5.4 months in the BSC arm, resulting in an incremental survival of 4.08 months or 0.34 years. Holmes et al. found an ICER of £13 863 per LYG for docetaxel 75 mg compared to BSC. In this study, the incremental survival was calculated by using an area under the curve (AUC) analysis, which resulted in an incremental survival of 3.82 months or 0.32 years. Cost estimates, if converted to 1999 Canadian Dollars, were similar to the cost estimates by Leighl et al. However, Holmes et al. did not include hospitalization costs or adverse events costs in their base-case analysis. In sensitivity analyses, the costs for toxicity treatments were varied between £0 and £301, but this was not done for the costs of hospitalization. In the original trial by Shepherd et al. a higher mean number of hospital days for the BSC group (7.3) was reported, compared to the docetaxel group (5.4) (50). Considering this difference in their analysis would increase the cost-effectiveness of docetaxel.

In the two remaining cost-effectiveness studies, docetaxel is considered as comparator for pemetrexed (45) and pemetrexed and erlotinib (39). Asukai et al. reported better outcomes and increased costs for pemetrexed. The resulting ICER of €23 967 per additional QALY for pemetrexed compared to docetaxel is well below cost-effectiveness threshold of €30 000 per QALY in Spain. Pemetrexed is associated with more chemotherapy costs, but less costs for adverse events, as they occurred less frequently in the pemetrexed arm. This also contributes favorably to the health-related quality of life of patients treated with pemetrexed. Quality of life estimates were based on utility values which were obtained from a study of 100 NSCLC patients. A utility decrement was obtained for each of the occurring adverse events, depending on the health state (stable

or response state). All unit costs were based on national databases (Spanish reference Database BOT; OBLIKUE) and resource use was estimated by expert opinion (45).
Finally, Carlson et al. evaluated the cost-effectiveness of docetaxel and pemetrexed as well as erlotinib, based on indirect comparisons as there was no head-to-head trial data available. Therefore, incremental analysis was only performed pairwise. Overall survival was assumed to be equal in all treatment arms, as well as progression free survival. When QALYs were taken as health outcome measure, erlotinib gave a 0.01 incremental QALY compared to docetaxel and pemetrexed, which was a result of less severe adverse events and the oral administration of erlotinib, versus intravenous administration of pemetrexed and docetaxel. In the cost-utility analysis, erlotinib dominated both docetaxel and pemetrexed. This is explained by the higher incidence of adverse events for docetaxel, and the higher chemotherapy costs for pemetrexed (39).
To summarize, docetaxel seems a cost-effective treatment option when compared to BSC. Although the two relevant studies are from different countries (UK and Canada), they were based on the same trial. As such, survival data and resource use can be assumed equal between the studies, and the allocation of costs by the investigators becomes critical. These studies show the influence of costing on cost-effectiveness results, as the impact of trial-based data input is eliminated (40;44). The adverse events associated with docetaxel were febrile neutropenia and neutropenia in three studies, which are both related to hospitalization, and therefore, were the main cost drivers for docetaxel (39;44;45). The fourth study did not take adverse events into account (40). Finally, pemetrexed was a more expensive drug than docetaxel, with less adverse events, in two independent studies, although each was performed in another country (39;45). Pemetrexed was cost-effective compared to docetaxel in one study (45).

Table 5. Overview of included clinical input and costs per study for second-line treatment

Study	Leighl[1] (44)	Holmes[1,2] (40)	Asukai (45)	Carslon[1] (39)	
				(DOC and PEM)	**ERL**
Parameter					
Survival (months)					
Mean	+	+	-	+*	+
Median	-	-	+	-	-
Progression free survival					
Mean	-	-	-	+*	+*
Median	-	-	+	-	-
Costs					
Chemotherapy	+	+	+	+	+
Other medications	+	+	+	+	+
Administration	+	+	+	+*	+
Hospitalization	+	-	+	+	+
Investigations/tests	+	-	+	+	+
Outpatient visits	+	?	+	+	+
Toxicity/ adverse events	+	-	+	+	+
Progression/terminal care	?	?	+	+*	+*

+, included in analyses; -, not included in analyses; ?, not clear whether included in analyses; +*, included, but assumed equal; DOC, docetaxel; PEM, Pemetrexed; ERL, erlotinib.

[1]Resource use is based on the same trial (shepherd)

[2] Only incremental costs presented, BSC is set at 0

Table 6. Detailed overview of results of those studies on second-line treatment which have docetaxel as one of the treatment arms.

Study, comparator	Costs			Survival (y)		
	DOC arm	comparator arm	incremental costs	DOC arm	comparator arm	incremental survival
Leighl et al. (44)				Mean survival		
BSC	$Can17 739	$Can6 935	$Can10 804	0.79	0.45	0.34
Holmes et al. (40)				Incremental survival		
BSC	£4 432	£0	£4 432	0.32	0.00	0.32
Asukai et al. (45)				Mean survival		
PEM	€32 343	€34 677	€-2 334	0.89	1.03	−0.14
Carlson et al. (39)				Overall survival		
PEM	$US39 104	$US43 759	$US−4 655	0.75	0.75	0.00
ERL	$US39 104	$US36 977	$US2 127	0.75	0.75	0.00

BSC = best supportive care; **ERL** = erlotinib; **PEM** = pemetrexed.

4

Discussion

In this report, the results of our two systematic reviews of the literature concerning the effectiveness and cost-effectiveness of docetaxel, gemcitabine, paclitaxel, pemetrexed, and vinorelbine are presented and discussed.

Quality of the evidence

The methodological quality assessment showed that the quality of the studies was acceptable, although a few items were consistently underreported. In addition, some shortcomings could not be scored with the assessment tool by Drummond et al. For example, there is no question that addresses the inclusion of all relevant cost items. In this review, we found that it was unclear in all of the studies whether costs for palliative care or terminal care were included. With respect to the quality of the modeling studies, we found estimates of the key parameters, model assumptions or calculations to be poorly reported. Preferably, economic evaluations would be more explanatory in their intents and methods. More detailed and transparent model descriptions would possibly permit better comparisons among studies, and as such, systematic reviews of economic evaluations could generate stronger evidence for policy makers (51).

Strengths and limitations

Although we searched three relevant databases, we may have missed studies. We have tried to minimize the risk of missing relevant studies by scanning the reference lists of all included studies. Studies were limited to those in the English and Dutch language, which may have precluded relevant studies published in different languages. Additionally, publication bias may have occurred, as industry-funded studies with unfavorable findings may not have been published.

For the purpose of this report we specifically restricted ourselves to economic evaluations conducting cost-utility analyses and/or cost-effectiveness analyses. Moreover, we restricted our selection to studies that considered the five third generation drugs among each other or in comparison to BSC. This inclusion criterion greatly reduced the number of initially selected studies. Although this resulted in a relatively small number of included studies, our strategy corresponds to our aim to find whether any one of the third generation agents is superior in terms of (cost)-effectiveness.

Discussion of the results

Regarding effectiveness, a number of issues were already covered by a recently published systematic review (3). Briefly said, there is evidence that chemotherapy in advanced NSCLC is more effective than best supportive care and that chemotherapeutic regimens containing third generation agents are more effective than regimens containing second generation agents. In addition, doublet chemotherapeutic regimens were found to be more effective than single agent therapy, while regimens consisting of a combination of three drugs did not improve the efficacy of doublets and worsened the toxicity associated with chemotherapy.

A conclusion on the possible superiority of one of the third generation drugs over the others could not be established by Goffin et al., due to contradicting evidence. Our update of the search by Goffin et al. resulted in an additional seven phase III trials, in which the effectiveness of the four agents of interest was compared in first-line treatment. The number of the included studies was small and the results were inconsistent. However, the lack of evidence to indicate superiority of one of the agents suggests comparable effectiveness. Without evidence of differences in effectiveness, the choice for a specific drug should be based on toxicity profiles and quality of life (QOL). Most of the studies reported quite different toxicity profiles among the agents. Quality of life, however, was not assessed in most studies.

In our systematic review concerning the cost-effectiveness of the four third generation drugs, eight studies were included covering first-line and second-line treatment as well

as maintenance therapy. It should be noted that we included pemetrexed in our systematic search, in addition to docetaxel, gemcitabine, paclitaxel, and vinorelbine. In first-line treatment, gemcitabine-cisplatin was a more cost-effective treatment option than paclitaxel-cisplatin in two studies (43;46). In addition, gemcitabine-cisplatin was more cost-effective than other regimens in one study (43), except for pemetrexed-cisplatin, which was more cost-effective than gemcitabine-cisplatin in the subgroup of non-squamous cell carcinoma population (41). In second-line treatment, docetaxel is a cost-effective treatment option compared to BSC in two studies (40;44). Additionally, pemetrexed is a cost-effective option compared to docetaxel in one study (45), but not in another study (39). At last, erlotinib was cost-effective compared to docetaxel and pemetrexed in one study (39).

Comparing the results of cost-effectiveness studies is difficult because of differences in country, perspective and year of publication (37;52). There is a wide range of factors that limit the generalizability of results, over time and between health systems and health care settings, including the context-dependency of recourse use and different decision contexts and budget constraints (51). The cost-effectiveness studies included in the present study differed for example in study design (trial-based versus model-based), time horizon, treatment dosage and infusion time. Model based studies (39;45) are difficult to compare because of different assumptions regarding model structure and different parameter values. E.g. Asukai et al. assumed that adverse events were mutually exclusive, while Carlson et al. considered only adverse events with an incidence greater than 5% and those requiring hospitalization. In addition, only grade 3 or 4 adverse events and corresponding disutilities were reported, while suffering from more than one grade 1 or 2 adverse event might be a considerable reduction of quality of life as well.

None of the included studies used a societal perspective for their analyses, although this is preferred in economic evaluations (37). However, this might not be relevant for patients in a severe stage of lung cancer: as the two-year survival probability of patients

in stage IIIB/IV is very low, they will probably not be able to return to work during their disease.

Conclusions

Due to the relatively small number of studies, conflicting evidence and methodological limitations, strong conclusions cannot be drawn. Nevertheless, we can provide some indications based on the available studies. Firstly, the lack of consistent evidence on superiority of one of the third generation agents over the others and the fact that most studies report similar efficacy suggests that these drugs may have comparable effectiveness. With the present knowledge, a choice for either of these drugs is thus best based on the toxicity profiles of each respective drug. Secondly, with respect to the costs of NSCLC treatment, it is evident that the main cost drivers are the costs of chemotherapy and the costs of hospitalization. The former is fixed; the latter can vary depending on the manner and duration of administration and the incidence of adverse events. This shows the toxicity profile is an important tool in the decision making process and therefore, research regarding toxicity profiles for each agent as well as the costs related to toxicity, such as hospitalization, is warranted.

Finally, we found that carrying out a cost-effectiveness study alongside a clinical trial in NSCLC appears not (yet) to be common research practice. As the cancer drugs are increasingly more expensive, taking the costs of health care into account is crucial to manage tight budgets.

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Appendices

Table 1. Search strategy for effectiveness of first-line chemotherapy in advanced NSCLC in PubMed.

Set	Search terms
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh] OR NSCLC[tiab] OR (lung[tiab] AND (cancer*[tiab] OR neoplasm*[tiab] OR carcinom*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab]) AND non[tiab] AND (advanced[ti] OR metastatic[ti]))
#2	"Paclitaxel"[Mesh] OR "docetaxel "[Substance Name] OR "gemcitabine "[Substance Name] OR "vinorelbine "[Substance Name] OR "pemetrexed "[Substance Name] OR "erlotinib "[Substance Name] OR "gefitinib "[Substance Name] OR paclitaxel[tiab] OR taxol[tiab] OR docetaxel[tiab] OR taxotere[tiab] OR gemcitabine[tiab] OR gemzar[tiab] OR vinorelbine[tiab] OR navelbine[tiab] OR pemetrexed[tiab] OR ALIMTA[tiab] OR erlotinib[tiab] OR tarceva[tiab] OR gefitinib[tiab] OR iressa[tiab]
#3	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies [pt] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw]) OR ((review[tiab] OR "Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]))
#4	#1 AND #2 AND #3
#5	#4 AND "2007/11/01"[Entrez Date] : "2010/09/27"[Entrez Date]
Final set	#5 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type]) Limits: English, Dutch

Figure 1. Flow-chart of the search and selection procedure of the effectiveness studies.

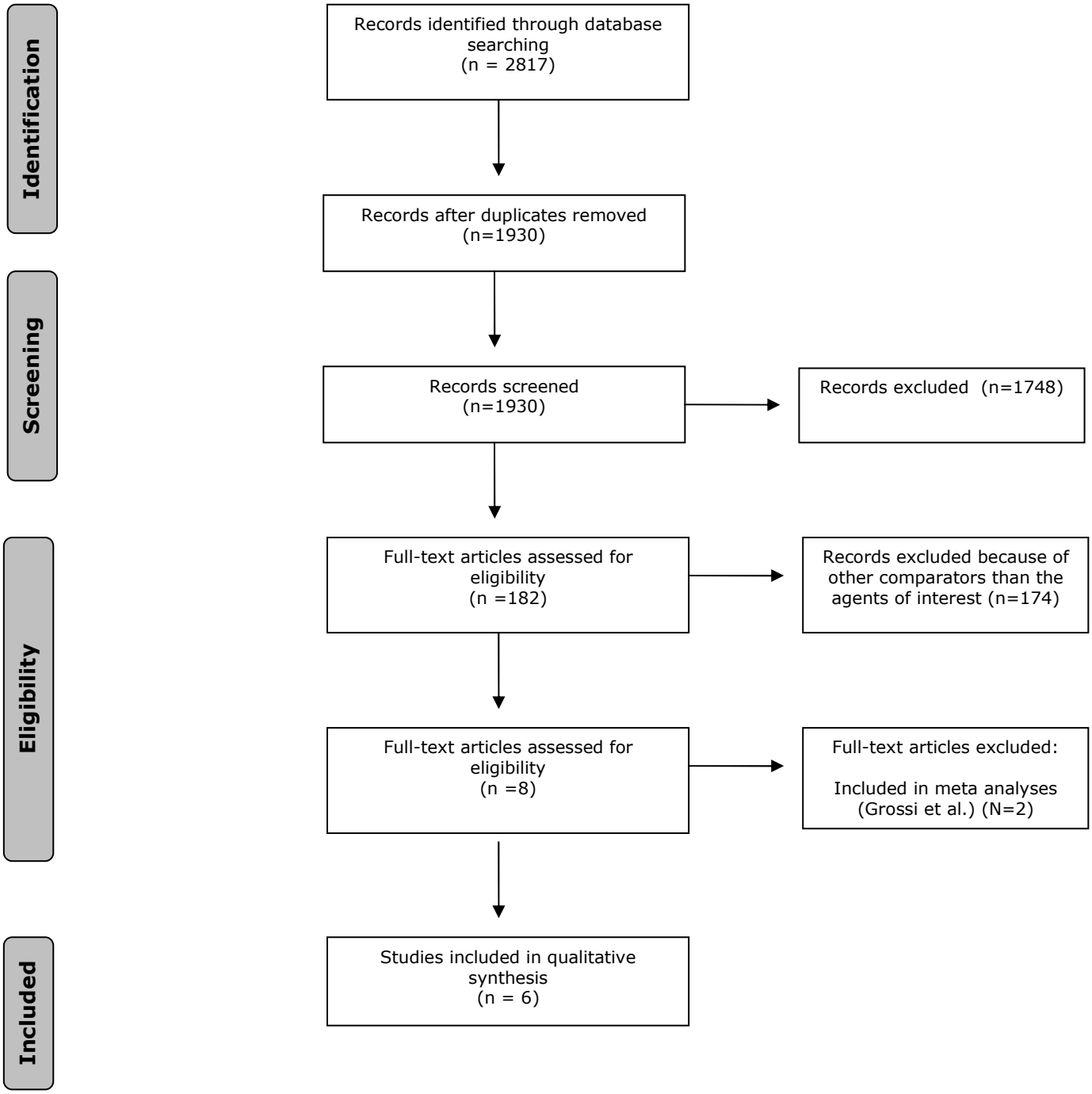


Table 2. Search strategy for cost-effectiveness of chemotherapy in advanced NSCLC in PubMed.

Set	Search terms
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh] OR NSCLC[tiab] OR (lung[tiab] AND (cancer*[tiab] OR neoplasm*[tiab] OR carcinom*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab]) AND non[tiab] AND (advanced[ti] OR metastatic[ti]))
#2	"Paclitaxel"[Mesh] OR "docetaxel "[Substance Name] OR "gemcitabine "[Substance Name] OR "vinorelbine "[Substance Name] OR "pemetrexed "[Substance Name] OR "erlotinib "[Substance Name] OR "gefitinib "[Substance Name] OR paclitaxel[tiab] OR taxol[tiab] OR docetaxel[tiab] OR taxotere[tiab] OR gemcitabine[tiab] OR gemzar[tiab] OR vinorelbine[tiab] OR navelbine[tiab] OR pemetrexed[tiab] OR ALIMTA[tiab] OR erlotinib[tiab] OR tarceva[tiab] OR gefitinib[tiab] OR iressa[tiab]
#3	"Costs and Cost Analysis"[Mesh] OR ((cost*[tiab] OR economic*[tiab]) AND (Effectiveness[tiab] OR efficiency[tiab] OR Benefit[tiab] OR Utility[tiab] OR Analys*[tiab] OR Evaluation[tiab] OR Burden[tiab])) OR "Quality adjusted"[tiab]
#4	#1 AND #2 AND #3
Final set	#4 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type]) Limits: English, Dutch

Figure 2. Flowchart of the search and selection procedure of cost-effectiveness

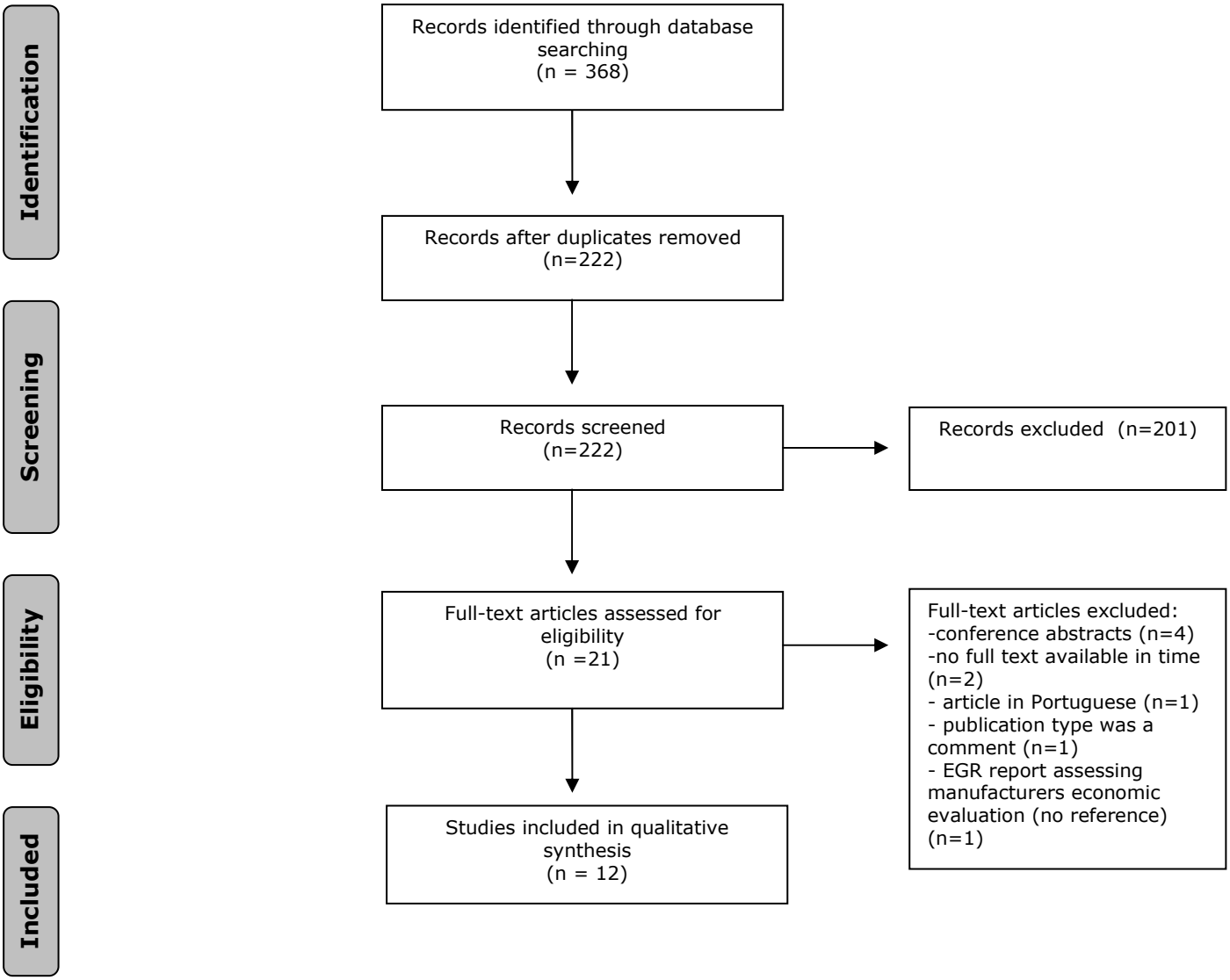


Table 3. Assessment of first-line studies

Study (1st author, year of publication)	Klein, 2009	Neymark, 2005	Lees, 2002	Maniadakais, 2007
Study design				
1. The research question is stated.	Y	Y	Y	Y
2. The economic importance of the research question is stated.	NC	Y	Y	Y
3. The viewpoint(s) of the analysis are clearly stated and justified.	Y	Y	Y	Y
4. The rationale for choosing alternative programmes or interventions compared is stated.	Y	Y	Y	Y
5. The alternatives being compared are clearly described.	Y	Y	Y	Y
6. The form of economic evaluation used is stated.	Y	Y	Y	Y
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Y	Y	Y	Y
Data collection				
8. The source(s) of effectiveness estimates used are stated.	Y	Y	Y	Y
9. Details of the design and results of effectiveness study are given (if based on a single study).	Y	Y	Y	Y
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Y	NA	NA	NA
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Y	Y	Y	Y
12. Methods to value benefits are stated.	Y	NA	NA	NA
13. Details of the subjects from whom valuations were obtained were given.	N	NA	NA	NA
14. Productivity changes (if included) are reported separately.	NA	NA	NA	NA
15. The relevance of productivity changes to the study question is discussed.	NC	NC	N	N
16. Quantities of resource use are reported separately from their unit costs.	N	Y	N	N
17. Methods for the estimation of quantities and unit costs are described.	Y	Y	Y	Y
18. Currency and price data are recorded.	N	Y	Y	Y
19. Details of currency of price adjustments for inflation or currency conversion are given.	N	Y	Y	N
20. Details of any model used are given.	Y	NA	NA	NA
21. The choice of model used and the key parameters on which it is based are justified.	Y	NA	NA	NA
Analysis and interpretation of results				
22. Time horizon of costs and benefits is stated.	Y	Y	NC	N
23. The discount rate(s) is stated.	Y	NA	NA	N
24. The choice of discount rate(s) is justified.	N	NA	NA	N
25. An explanation is given if costs and benefits are not discounted.	NA	Y	Y	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	N	Y	N	Y
27. The approach to sensitivity analysis is given.	Y	Y	Y	NA
28. The choice of variables for sensitivity analysis is justified.	Y	Y	Y	NA
29. The ranges over which the variables are varied are justified.	N	Y	NC	NA
30. Relevant alternatives are compared.	Y	Y	Y	Y
31. Incremental analysis is reported.	N	N	NA	Y
32. Major outcomes are presented in a disaggregated as well as aggregated form.	N	Y	Y	Y
33. The answer to the study question is given.	Y	Y	Y	Y
34. Conclusions follow from the data reported.	Y	Y	Y	Y
35. Conclusions are accompanied by the appropriate caveats.	Y	Y	N	N

Y, yes; N, no; NA, not appropriate; NC, not clear.

Table 4. Assessment of second-line studies

Study (1st author, year of publication)	Leighl, 2002	Holmes, 2004	Asukai, 2010	Carslon, 2007	Klein, 2010
Study design					
1. The research question is stated.	Y	Y	Y	Y	Y
2. The economic importance of the research question is stated.	Y	Y	Y	Y	NC
3. The viewpoint(s) of the analysis are clearly stated and justified.	Y	Y	Y	Y	Y
4. The rationale for choosing alternative programmes or interventions compared is stated.	Y	Y	Y	Y	Y
5. The alternatives being compared are clearly described.	Y	Y	Y	N	Y
6. The form of economic evaluation used is stated.	Y	Y	Y	Y	Y
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Y	Y	Y	N	Y
Data collection					
8. The source(s) of effectiveness estimates used are stated.	Y	Y	Y	Y	Y
9. Details of the design and results of effectiveness study are given (if based on a single study).	Y	Y	Y	NA	NA
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA	NA	NA	Y	Y
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Y	Y	Y	Y	Y
12. Methods to value benefits are stated.	NC	NA	Y	Y	NA
13. Details of the subjects from whom valuations were obtained were given.	Y	NA	N	Y	NA
14. Productivity changes (if included) are reported separately.	NA	NA	NA	NA	NA
15. The relevance of productivity changes to the study question is discussed.	N	N	Y	NA	N
16. Quantities of resource use are reported separately from their unit costs.	Y	Y	N	Y	N
17. Methods for the estimation of quantities and unit costs are described.	Y	Y	Y	Y	Y
18. Currency and price data are recorded.	Y	Y	Y	Y	Y
19. Details of currency of price adjustments for inflation or currency conversion are given.	Y	N	Y	Y	Y
20. Details of any model used are given.	NA	NC	Y	Y	Y
21. The choice of model used and the key parameters on which it is based are justified.	NA	NC	Y	N	Y
Analysis and interpretation of results					
22. Time horizon of costs and benefits is stated.	Y	Y	Y	Y	Y
23. The discount rate(s) is stated.	NA	NA	Y	Y	Y
24. The choice of discount rate(s) is justified.	NA	NA	N	Y	N
25. An explanation is given if costs and benefits are not discounted.	Y	Y	NA	NA	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	NC	N	Y	N	N
27. The approach to sensitivity analysis is given.	Y	Y	Y	Y	Y
28. The choice of variables for sensitivity analysis is justified.	Y	Y	N	Y	N
29. The ranges over which the variables are varied are justified.	NC	Y	Y	Y	N
30. Relevant alternatives are compared.	Y	Y	Y	Y	Y
31. Incremental analysis is reported.	Y	Y	Y	Y	N
32. Major outcomes are presented in a disaggregated as well as aggregated form.	Y	Y	Y	N	N
33. The answer to the study question is given.	Y	Y	Y	N	Y
34. Conclusions follow from the data reported.	Y	Y	Y	Y	NC
35. Conclusions are accompanied by the appropriate caveats.	Y	Y	Y	Y	Y

Y, yes; N, no; NA, not appropriate; NC, not clear.

Table 5. Assessment of modeling studies (first-and second-line treatment)

Dimension of quality	Question(s) for critical appraisal	Klein 2009	Asukai 2010	Carlson 2005	Klein 2010
STRUCTURE (S)					
S1: Statement of decision problem/objective	Is the decision problem clear?	Y	Y	Y	Y
	Is the objective of the evaluation and model specified consistent with the stated decision problem?	Y	Y	Y	Y
	Is the primary decision maker specified?	Y	N	N	Y
S2: Statement of scope/perspective	Is the perspective of the model stated clearly?	Y	Y	Y	Y
	Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y
	Has the scope (context) of the model been stated and justified?	Y	Y	Y	Y
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	Y	Y	Y
S3. Rationale for structure	Has the evidence regarding the model structure been described? Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	N	N	N	N
	Are the sources of data used to develop the structure of the model specified?	N	N	N	N
	Are the (causal) relationships described by the model structure justified appropriately?	Y	N	N	N
S4: Structural assumptions	Are the structural assumptions transparent and justified?	Y	N	N	N
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	?	Y
S5: Strategies/comparators	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y
	Have all feasible and practical options been evaluated?	Y	N	Y	Y
	Is there justification for the exclusion of feasible options?	NA	Y	NA	NA
S6: Model type	Is the chosen model type appropriate given the decision problem?	Y	Y	N	Y
S7: Time horizon	Is the time horizon of the model sufficient to reflect all important differences between options?	Y	Y	Y	Y
	Is the time horizon of the model, and duration of treatment and treatment effect described and justified?	Y	Y	Y	Y
S8: Disease states/pathways	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	?	Y
S9: Cycle length (For discrete time models)	Is the cycle length defined and justified in terms of the natural history of disease.	N	N	NA	Y

DATA (D)

D1: Data identification	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y	Y
	Where choices have been made between data sources, are these justified appropriately?	NA	NA	NA	NA
	Has particular attention been paid to identifying data for the important parameters in the model?	Y	Y	Y	Y
	Are systematic methods used to identify the key parameters?	N	N	N	N
	Has the quality of the data been assessed appropriately?	N	?	N	N
	Where expert opinion has been used, are the methods described and justified?	NA	Y	NA	NA
D2: Pre-model data analysis	Are the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	?	?	?	?
D2a: Baseline data	Is the choice of baseline data described and justified?	Y	?	Y	Y
	Are transition probabilities calculated appropriately?	?	?	?	?
	Has a half cycle correction been applied to both cost and outcome?	?	?	NA	?
	If not, has this omission been justified?	NA	N	NA	NA
D2b:Treatment effects	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	Y	NA	Y	NA
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	NA	NA	NA
	Have alternative assumptions been explored through sensitivity analysis?	Y	Y	NA	NA
	Have assumptions regarding the continuing effect of treatment once treatment has been completed been documented and justified?	NA	Y	NA	Y
	Have alternative assumptions been explored through sensitivity analysis?	NA	NA	NA	N
D2c: Quality-of-life weights (utilities)	Are the utilities incorporated into the model appropriate?	?	Y	Y	NA
	Is the source for the utility weights referenced?	Y	Y	Y	NA
	Are the methods of derivation for the utility weights justified?	?	Y	Y	NA
D3: Data incorporation	Have all data incorporated into the model been described and referenced in sufficient detail?	Y	Y	Y	Y
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	NA	NA	NA	NA
	Is the process of data incorporation transparent (i.e. point estimate or distribution)?	Y	Y	Y	Y

	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	NA	Y	N	N
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	Y	Y	Y
D4a: methodological	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	N	N	N	N
D4b: structural	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	N	N	N
D4c: heterogeneity	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Y	N	N	Y
D4d: parameter	Are the methods of assessment of parameter uncertainty appropriate?	Y	Y	Y	Y
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	Y	Y	N

CONSISTENCY (C)

C1: Internal consistency	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	N	N	N	N
C2: External consistency	Are the conclusions valid given the data presented?	Y	Y	N	Y
	Are any counterintuitive results from the model explained and justified?	NA	NA	NA	NA
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	NA	NA	NA
	Have the results of the model been compared with those of previous literature and any differences in results explained?	Y	NA	Y	Y

Y, yes; N, no; NA, not appropriate; ?, unknown/not reported.